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Original Article

Sex Differences in Elderly Patients Using Patient Controlled Analgesia in the Postoperative Period: A Retrospective Database Analysis☆

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SUMMARY

Background: Sex differences in pain perception exist in humans. This study aimed to search whether sex differences also existed in patient controlled analgesia (PCA) among elderly populations.
Methods: Patients' information was retrieved from a quality-insurance database from a period of 2 years. Demographic characters, types of PCA mode, consumptions of PCA drugs on postoperative Day 1, all PCA-related complications, visual analogue scale in bed rest, daily activities, and coughing, surgical sites, American Society of Anesthesiologists physical status, and satisfaction to PCA were all analyzed.
Results: A total of 1441 women (71.6 ± 8.4 years) and 730 men (70.9 ± 7.7 years) were analyzed. Elderly women had higher incidences of nausea, vomiting, vertigo, inappropriate sensory and motor blockages, as well experiencing more pain in bed rest and daily activities. Elderly men had more pain experience while coughing but had higher satisfactions to PCA.
Conclusion: Several important sex differences existed in the elderly patients when utilizing PCA as pain management. More concern should be drawn to these differences to minimize PCA-related complications and to avoid the potential hazard of PCA in vulnerable elderly patients. Generalization of this application in other constitutions requires further studies.

1. Introduction

Several experimental and clinical studies have reported an age-related decrease in pain perception, but whether the decrease results from the aging process or other age-associated conditions remains unclear[1,2]. Although reduced pain perception exists in elderly people, postoperative wound pain, which often severely interferes with the respiratory and cardiovascular system, still plays an important role in the postoperative period. A well-prepared pain strategy is especially imperative in these vulnerable patients. With much quicker drug deliveries, easy titration to desired analgesia effects, and less drug overdose concerns, patient-controlled analgesia (PCA) is considered superior to conventional intramuscular opiates injection. Although safer and more effective than conventional opiate injections in pain relieving, the use of PCA still carries lots of potential adverse events, ranging from nausea, vomiting, vertigo, and skin itching, to life-threatening conditions, including respiratory and conscious depress; and more attention to these complications should be paid, especially in elderly patients. In the past decade numerous studies in animals and humans have indicated sexual dimorphism in many regions of the central nervous system[3–5], so it is not surprising that there were lots of experiments drawing their focus on contributions of sex to pain perception and analgesia—and many studies indeed support sex difference mechanisms[6–9]. Although many animal studies have confirmed the fact that opioids act more efficaciously in men, in humans it is not so clear regarding the presence of sex differences in opioid effects[9,10]. In this study, our goals were to confirm the safety of a PCA device in an elderly population, to find whether there are sex differences in PCA-related complications, in opiates and local analgesics requirements, and in the satisfaction to PCA devices.

2. Materials and methods

This retrospective analysis is based on a quality-assurance system for following-up patients that utilized a PCA to ameliorate

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postoperative pain in our hospitals. These patients could have had a PCA device either from an intravenous route or an epidural catheter, as suggested by the surgeons and anesthetists for more pain relief and less unavoidable drug-related complications.

All patients received regular postoperative checks for at least 3 days. The volumes of delivered drugs and other drugs acting as analgesic adjuvants or as interventions for PCA-related complications were totaled. Complications being considered directly related to PCA were carefully searched and surveyed. PCA-related side events included respiratory and conscious depress, skin itching, urine retention, nausea, vomiting, vertigo, and inappropriate blockage of motor and sensory functions of extremities. The respiratory depression effect of PCA was monitored by spontaneous respiratory rate, and set to be alarming whereas the rate was below eight cycles/min. The conscious was classified as follows: Level I, an alert state; Level II, drowsy but immediately responding to commands or stimulations; Level III, a deeper drowsy state with slowly responding to commands and stimulations, and level IV, loss of conscious without any response to commands and stimulations.

The efficiency of PCA was evaluated utilizing an interactive visual analogue pain scale with 100 for the worst experienced pain and 0 for almost free of pain, and we evaluated the wound pain in three dissociated conditions: bed rest, coughing, and daily activities (such as walking in the ward), respectively. For the purpose of further studies, some particular patients' demographics data comprising age, sex, body weight, body height, and American Society of Anesthesiologists (ASA) physical status were all registered in the database. Other collected items included surgical sites, general or regional anesthesia, and patients' satisfaction with the PCA.

All the database items were analyzed using SPSS 21.0 (IBM SPSS Inc., New York, America), with an independent-sample *t*-test procedure for testing difference of means of scale variables, and crosstabs procedure with options of Chi-square test or Fisher's exact test to find differences in proportions for categorical variables. The scale variables were reported in terms of mean ± standard deviation and categorical variables in terms of number and percentage. Statistical significance was set at $p < 0.05$.

The study protocol was approved by the Institute Review Board of our hospital[11,12].

3. Results

From January 1, 2012 to December 31, 2013, our quality-assurance database collected information of 7317 patients; among them, the female group surprisingly dominated in numbers (5791–1526). In the same population, the elderly group (age > 60 years) comprised 2171 cases, also with an accordingly high women to men ratio (1441:730).

In the 2171 elderly patients, the age difference between women and men was not significant (71.6 ± 8.4 vs. 70.9 ± 7.7; $p = 0.06$), but the elderly men were superior to the elderly women in terms of body weight (66.5 ± 25.5 kg vs. 59.5 ± 11.3 kg; $p < 0.001$) and body height (165.3 ± 5.9 cm vs. 153.4 ± 13.2 cm; $p = 0.001$).

Among the elderly patients, 994 women and 433 men chose intravenous morphine as a pain relieving drug, and in elderly men the total volume of morphine delivered at the 1st postoperative day was significantly more than in the elderly women (25.51 ± 24.30 mg vs. 21.91 ± 20.54 mg; $p = 0.007$), but this difference disappeared when body weight was considered (0.45 ± 0.53 mg/kg vs. 0.37 ± 0.34 mg/kg; $p = 0.271$). In the other 241 men and 374 women, the PCA devices pumped the local anesthetic levobupivacaine into the epidural space. The differences of totally pumped volumes of levobupivacaine in elderly men and women were not statistical significance (141.53 ± 49.96 mL vs. 138.45 ± 41.99 mL; $p = 0.402$), but when the body weights were included in the calculation, we found that the elderly female group took higher volumes than the elderly male group did (2.41 ± 0.83 mL/kg vs. 2.26 ± 0.90 mL/kg; $p = 0.37$).

The sex differences of responsiveness to PCA were found. Elderly women experienced more pain than elderly men during bed rest and in daily activities (19.69 ± 13.45 vs.17.57 ± 13.06; $p = 0.001$; 43.77 ± 15.68 vs. 39.99 ± 16.71; $p = 0.001$; respectively; Table 1), but the elderly men had stronger painful sensations than elderly women when coughing (46.81 ± 22.43 vs. 42.11 ± 25.34; $p = 0.001$). After all, with less PCA-related complications and a lower visual analogue pain scale than elderly women, the elderly men were more satisfied with PCA than the elderly female group (92.8% vs. 85.7%; $p = 0.001$; Table 2).

Among all patients, there was no PCA-related respiratory depression reported and only five patients (three women and two men) developed mild drowsiness which only needed close monitoring. Approximately 24.7% of the patients complained of nausea, with women being more vulnerable than men (29.8% vs. 14.5%; $p = 0.001$; Table 3), and 14.3% of the patients complained of vomiting, with women also having a higher incidence rate (18.7% vs. 5.5%; $p = 0.001$). Skin itching was seldom complained of (2.4%), and no sex difference was found (women 2.9% vs. men 1.4%; $p = 0.105$). Due to the Foley tube being a routine setting after most surgical procedures in elderly patients, the real incidence of urine retention could not be accurately estimated. Only 0.21% was reported and no sex difference was found (women 0.2% vs. men 0.3%; $p = 0.067$).

Elderly women complained of inappropriate sensory blocks more than the elderly men (9.6% vs. 3.7%; $p = 0.009$; Table 4). They also complained of inappropriate motor blocks more than the men (6.9% vs. 1.5%; $p = 0.005$). The total incidences of inappropriate sensory and motor blocks were 7.2% and 4.7%, respectively.

The elderly women and men presented much different varieties of diseases that needed surgical intervention ($p = 0.001$; Table 5). In the female group, the surgical interventions involved mainly the lower extremities (44.1%) and lower abdomen (25.1%), whereas in the male group, lower extremities (27.8%) and upper abdomen (22.3%) were the leading two areas, followed by the lower abdomen (19.9%).

The ASA physical status is a standard and routinely used measure to predict a patient's risk for anesthesia and surgery, with a higher grade implying a higher risk. Above half (52.3%; Table 6) of the elderly men were graded as ASA III (moderate risk) and the proportion was significantly higher than in the female group (44.4%; $p = 0.002$). Most of our patients needed general anesthesia for their surgical procedures, with more men needing general anesthesia than the female group (76.3% vs. 63.0%; $p = 0.001$).

4. Discussion

In our patients, women are much more desirous of PCA than men, and in the elderly group, the female to male ratio was near 2:1,

Table 1
Comparisons of visual analog scale of elderly patients in bed rest, daily activities, and coughing.

	Group	*n*	Mean ± SD	*p*
Bed rest	F	709	19.69 ± 13.45	0.001
	M	414	17.57 ± 13.06	
Daily activities	F	709	43.77 ± 15.68	0.001
	M	1425	39.99 ± 16.71	
Coughing	F	528	42.11 ± 25.34	0.001
	M	829	46.81 ± 22.43	

F = female; M = male; SD = standard deviation.

Table 2
Distribution of satisfaction degrees to patient controlled analgesia in elderly women and men in a complete postoperative period.

		Women, *n* (%)	Men, *n* (%)	Total, *n* (%)*
Satisfactory degrees	I	148 (10.3)	107 (14.7)	255 (11.7)
	II	1087 (75.4)	570 (78.1)	1657 (76.3)
	III	186 (12.9)	30 (4.1)	216 (9.9)
	IV	6 (0.4)	2 (0.3)	8 (0.4)
	V	0 (0)	0 (0)	0 (0)
	VI	14 (1.0)	21 (2.9)	35 (1.6)
Total		1441	730	2171

Satisfactory level: I = very much satisfied; II = satisfied; III = acceptable; IV = dissatisfied; V = severely unacceptable; VI = no comments available.
* $p = 0.001$, Chi-square.

and even more in the whole population. The factor that women present more demanding for PCA than men can't simply be explained by the psychosocial factors contributing substantially to pain perception in humans that may differentially influence pain in men and women[13], and we could not find other studies to support this sex difference in PCA favor. There was another interesting finding in that the elderly women who took PCA for pain relief, 44.1% of them received surgical interventions in their lower extremities that are generally considered to be less pain-intensive procedures than abdomen and thoracic surgeries. However, 55.5% of elderly men underwent very painful surgeries, and only 39.6% of women had surgeries involving these sites. Further studies will be needed to explain this discrepancy between PCA demanding and intensities of surgical wound pain among men and women.

Although the animal studies revealed evidence of opioids acting more efficaciously in males, human studies did not provide clear confirmation in the presence and direction of any sex effect[13–17]; and two studies that specifically focused on the interaction between age and sex reported the disappearance of sex differences at age > 60 years[18,19]. By contrast, other studies examining the sex effect of opioids in men and women at postmenopausal ages (> 50 years) did find a sex effect[20]. The postoperative morphine requirement showed no sex differences in our elderly group if the body weight was included in the calculation (0.45 ± 0.53 mg/kg vs. 0.37 ± 0.34 mg/kg; $p = 0.27$), whereas the total amount of morphine is significantly higher in men (25.5 ± 24.3 mg vs. 24.9 ± 20.5 mg; $p = 0.004$). Most studies in humans did not measure the opioid concentration in plasma because women have a greater body fat percentage and most opioids are relatively lipophilic; therefore, it may be assumed that plasma opioid concentration differed between women and men and with lower concentration in womens[20]. In men, the mean percentage body fat ranged from 22.9% at age 16–19 years to 30.9% at age 60–79 years. In women, the mean percentage body fat ranged from 32.0% at age 8–11 years to 42.4% at age 60– 79 years[21]. These pharmacokinetics and physical differences in sex suggest that we may underestimate the true magnitude of the sex difference in opioid analgesia. We also cannot omit that in our elderly population, more men (55.5%) underwent more pain-intensive procedures than the women (39.6%); therefore we could not simply draw a conclusion that according to the equal delivered dosage of an opioid, there is no sex difference in opioid requirement in the postoperative period.

Compared with intravenous morphine, studies focusing on sex differences in epidural PCA for postoperative pain are rare[22]. Although being a challenging and time-consuming technique, thoracic epidural PCA was the better choice for blocking postoperative pain in thoracic and upper abdomen surgeries. Instead of morphine, local anesthetics are pumped into the epidural space to produce nerve blockage. In our hospital, levobupivacaine is the drug of choice due to its low cardiovascular and respiratory toxicities. In our elderly patients, there was no sex difference in the total volume of levobupivacaine delivered, but when the dosage is based on body weight, a sex difference of levobupivacaine dosage did exist. Schnabel et al[22], in a large population following-up program, reported a result which is incompatible with our findings. In their epidural PCA research, women showed a significantly lower total epidural PCA consumption compared with men, and a higher incidence of vomiting and motor blockade in women to discourage them from PCA were their explanations to this phenomenon. There are two factors that could explicate why our results are entirely different from theirs: (1) our study focused only on elderly people. The mean age of our women was 71.6 ± 9.4 years, compared with 52.42 ± 17.69 years of their female population. Although their study included a full spectrum of ages, and the younger the women the higher incidence of nausea and vomiting, this would lead to a decrease in requirement of PCA in their younger women. The second factor may be because of the slow onset time of levobupivacaine, a basal infusion mode was always setup in our patients for improving the pain relieving effects, and this default background infused dose may contribute to a large portion of total consumed volumes and resulted in a false higher dosage demanding in elderly women and more PCA-related complications would also ensue in them.

Although, in our elderly patients with mean ages > 70 years and mean morphine consumption ~25 mg at postoperative Day 1, there were only five patients (three women and two men) developing mild drowsiness which only needed close monitoring, and no other life-threatening complication was reported. It should be emphasized that in our population, 44.4% women were graded as ASA III

Table 3
Postoperative complications associated with intravenous patient controlled analgesia in elderly women and men.

Complications		Urine retention, *n* (%)		Vomit, *n* (%)		Nausea, *n* (%)		Itching, *n* (%)		Vertigo, *n* (%)	
Degrees		F	M	F	M	F	M	F	M	F	M
I	*n*	164	74	1153	664	1155	637	1371	693	996	601
	%	11.5	10.5	81.3	94.5	81.5	90.6	97.1	98.6	70.2	85.5
II	*n*	1	0	145	27	227	63	30	8	396	98
	%	0.1	0	10.2	3.8	16.0	9.0	2.1	1.1	27.9	13.9
III	*n*	2	2	115	11	33	2	11	2	24	3
	%	0.1	0.3	8.1	1.6	2.3	0.3	0.8	0.3	1.7	0.4
IV	*n*	1255	630	5	1	2	1	0	0	3	1
	%	88.3	89.2	0.4	0.1	0.1	0.1	0	0	0.2	0.1
p		0.677		0.001		0.001		0.105		0.005	

IV in urine retention = usage of Foley tube.
F = female; M = male; I = free of symptoms; II = completely free of symptoms after medical interventions; III = symptoms not improving much after medical interventions; IV = symptoms without any improving even after aggressive medical interventions.

Table 4
Postoperative complications associated with epidural patient controlled analgesia in elderly women and men.

Complications	ISB, *n* (%)		IMB, *n* (%)	
Degrees	F	M	F	M
I	369 (90.4)	263 (96.3)	380 (93.1)	269 (98.5)
II	34 (8.3)	10 (3.7)	26 (6.4)	4 (1.5)
III	5 (1.2)	0 (0)	2 (0.5)	0 (0)
IV	0 (0)	0 (0)	0 (0)	0 (0)
p	0.009		0.005	

I = free of symptoms; II = completely free of symptoms after medical interventions; III = symptoms not improving much after medical interventions; IV = symptoms without any improving even after aggressive medical interventions; ISB = inappropriate sensory blockage; IMB = inappropriate motor blockage; M = male; F = female.

Table 5
The distribution and proportion of surgical sites in elderly women and men.

Surgical site		Others	UE	LE	UA	LA	Back	Chest	Neck	Face
F	*n*	31	43	635	121	362	150	97	9	2
	%	2.2	3.0	44.1	7.8	25.1	10.4	6.7	0.65	0.1
M	*n*	19	10	203	163	145	77	97	9	7
	%	2.6	1.4	27.8	22.3	19.9	10.5	13.13	1.2	1.0

* $p = 0.001$ Chi-square.
F = female; LA = lower abdomen; LE = lower extremities; M = male; UA = upper abdomen; UE = upper extremities.

(with significant systemic diseases that affected their daily lives) and the proportion was even higher in men (52.3%). However, according to our result, it is an objective fact that with careful management, PCA devices were safe and practicable in elderly patients suffering systemic comorbidities. However, the incidence of other PCA-related adverse effects were much higher and women were always more vulnerable to these side effects than men, except with urine retention. The postoperative nausea and vomiting (PONV) are not only PCA related, but also closely related to surgical sites (more in abdomen procedures than others), anesthesia techniques (more after general anesthesia than regional anesthesia), anesthesia agents (more in inhalation agents than intravenous agents), and sex (more in women than men). In our study group, 42.2% men received surgical procedures in the abdomen, but only 32.9% of women had surgical procedures in the abdomen. Also 76.3% of men needed general anesthesia to undergo their surgeries—a much higher proportion than women (63.0%). If the above two factors that favor the occurrence of PONV were considered, we should admit that the true sex difference in PCA-related PONV was underestimated in our study. The elderly women also suffered more improper sensory and motor blockages than men. This difference can be explained well by the fact that women took more local anesthetics than the men, but we should also note that the elderly men in our study had more upper abdomen (22.3% vs. 7.8%) and thoracic surgeries (13.3% vs. 6.7%) that needed an epidural inserted from the thoracic spine of which physical location less likely produces improper sensory and motor blockage. Elderly women had more surgeries in the lower extremities (44.1% vs. 27.8%) and lower abdomen (25.1% vs. 19.9%) that required an epidural catheter set in the lumbar spine of which physical location may unfortunately be more likely to produce inappropriate sensory and motor blockage.

Table 6
The distribution and proportion of American Society of Anesthesiologists (ASA) grades in elderly women and men.

ASA grades		I	II	III	IV	V
F	*n*	54	747	640	0	0
	%	3.7	51.8	44.4	0	0
M	*n*	20	328	382	0	0
	%	2.7	44.9	52.3	0	0

* $p = 0.002$, Chi-square.
ASA grade I = healthy, no systemic disease; II = mild systemic disease; III = significant systemic disease; IV = systemic disease with life-threaten; V = death within 24 hours with or without surgical intervention; F = female; M = male.

Our study found that elderly women complained of stronger pain experiences than elderly men when they were in bed rest and with mild activities, despite the fact that the morphine requirements in the two groups were equal and the requirements of local anesthetics in epidural PCA were even higher in elderly women.

Several studies also reported higher pain suffering in women utilizing PCA in the postoperative period[19,22–25], but there were no age-limited criteria in their study population and two of the studies suggested that a sex difference is even less relevant in older patients, regardless of the analgesic regimen[19,22]. Why could the women tolerate more wound pain than men? One possible explanation is that the women did not want more analgesics because they are comparably satisfied with a lower degree of pain reduction and the more opioids they take, the more complications they suffer[20]. Is education also contributing to the attitude of women toward the dosage restriction of PCA? In Taiwan, the sex difference of educational attainment is more significant in the old-age population. In women aged > 65 years, only 15.79% of them had educational attainment above elementary school, compared with 40.14% of men in the same age population[26], and the more defects in educational attainment, the more misunderstandings of opioid addiction; this surely leads to a conclusion that elderly women have much more fear than men regarding the development of an opioid addiction if they do not restrict their morphine demands, even though they actually experienced more pain than men. Regardless of the less pain suffering when in bed and movements, our elderly males surprisingly presented a higher pain scale when they were coughing. At first this finding confused the other results that support women always being more vulnerable to wound pain; but if we considered the fact that 55.5% of elderly men had their surgeries in the chest and abdomen, these areas would become tender in a coughing movement, and only 39.6% of elderly women's wounds were in such locations, the finding would be more reasonable.

In conclusion, not surprising, with more adverse effects and higher pain sufferings, the satisfaction to PCA in elderly women were lower than in elderly men. However, the even more important fact is that the numbers of women who wanted to use PCA were much larger than the numbers of men. These findings in this study could provide anesthetists many informative clues regarding sex differences in elderly populations to modify the drug regimen according to patients' surgical interventions, to choose a better PCA mode to prevent improper sensory and motor blockages, and finally, to construct more simple and complete directions regarding PCA to elderly women with lower educational attainments.

4.1. Limitations

We enrolled patients with the limitation of ages > 60 years, but all other similar studies always allow a full spectrum of ages. This design difference may lead to an unavoidable bias when comparing our results with others. Due to anesthesia techniques, anesthesia agents, surgeries, and patient populations always being regionally specific, we must be very careful in generalizing our study findings to other applications.

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